REMARKS

Applicants have amended the specification to include material incorporated by reference in the application, as filed. Applicants' response is accompanied by a Declaration of Jane T. Gunnison, applicants' attorney, stating that the amendatory material consists of the same material incorporated by reference in the instant application.

Applicants have canceled claim 1, without prejudice, amended claims 2 and 3 and have added claims 46 and 47. Upon entry of the amendments, claims 2, 3, 46 and 47 will be pending in the application.

Specifically, applicants have added claim 46, which corresponds substantially to claim 1 and more fully describes the transgenic mouse used in the claimed method. Claim 47 is directed to a method for producing an antigen-binding fragment of an immunoglobulin, wherein said fragment comprises a fully human variable region. Support for this claim may be found throughout the specification, for example at page 8, lines 19-28 and page 12, lines 5-13.

None of these amendments adds new matter. Applicants request entry of the amendments and reconsideration of the claims.

Rejection Under 35 U.S.C. § 1.112, First Paragraph

Claims 1-3 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Specifically, the Examiner asserts that the specification does not disclose a transgene with sequences necessary for class switching to human gamma isotypes. The Examiner further asserts that the specification does not disclose how to produce immunoglobulin analogs in mice or mice having only the variable region of endogenous immunoglobulin loci inactivated. In view of the claim amendments, applicants traverse.

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Claims 2, 3, 46 and 47, as amended, explicitly state that the transgenic mouse utilized in the claimed methods does not contain a human gamma constant region. The claims recite a transgenic mouse comprising a human chromosome fragment that includes a human Cμ gene but ends within a human Cδ gene. Further, none of the amended claims recites the production of a human immunoglobulin analog in a transgenic mouse or endogenous immunoglobulin loci inactivated only with respect to the variable region. Accordingly, the rejection under § 112, first paragraph should be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3 stand rejected under 35 U.S.C. § 112, second paragraph, as "vague and unclear". Specifically, the Examiner asserts that the metes and bounds of the phrase "analog thereof" are indeterminate. In view of the claim amendments, applicants traverse.

None of the claims, as amended, contain the phrase "analog thereof". Claim 47 and the claims that depend therefrom refer instead to an antigen-binding fragment of an immunoglobulin comprising a fully human variable region. The metes and bounds of claim 47 would be clear to a person of ordinary skill in the art. Accordingly, the rejection under § 112, second paragraph should be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as "unpatentable" over United States patent 5,545,807 (Surani et al.) ("Surani "), taken with M. Bruggemann et al., "Repertoire Of Monoclonal Antibodies With Human Heavy Chains From Transgenic Mice," *Proc. Natl. Acad. Sci.*, 86, pp. 6709-6713 (1989) ("Bruggemann") and United States patent 5,591,669 (Krimpenfort et al.) ("Krimpenfort")

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In the Examiner's view, Surani discloses transgenic mice having inserted in their genomes DNA comprising human VH, human D, human JH segments and human Cδ segments; Bruggemann discloses the desirability of producing human immunoglobulins in a mouse incapable of expressing endogenous mouse immunoglobulins; and Krimpenfort discloses inactivation of endogenous mouse immunoglobulin gene expression by homologous recombination.

The Examiner concludes that it would have been obvious to one of ordinary skill to modify the mouse of Surani, by "knocking out" endogenous immunoglobulin expression as suggested by Bruggemann and Krimpenfort. In view of the claim amendments, applicants traverse.

Claims 2, 3, 46 and 47 are directed to methods for producing an immunoglobulin that is specific for a desired antigen and that comprises a fully human variable region. The methods utilize a transgenic mouse whose genome comprises a SpeI-SpeI fragment of human chromosome 14, said fragment being found within a human immunoglobulin heavy chain locus. That fragment is an unrearranged germline fragment of a human Ig heavy chain locus. The DNA fragment recited in the claims contains all of the human D segment genes, all of the human JH segment genes, a human Cμ gene and at least a portion of a human Cδ gene and the sequences in between. The claimed methods, thus utilize a transgenic mouse containing a human IgH germline fragment spanning approximately 85-100 kb. The IgH gene segments on that fragment have essentially the same spacial relationship to each other as they do on human chromosome 14 (i.e., they are in germline configuration).

In contrast, none of the cited documents teaches or suggests a transgenic mouse containing such a fragment. Surani and Bruggemann refer only to mice containing a mixture of human and mouse Ig sequences. Further, those human and mouse sequences are separately cloned and then engineered to

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form a "minigene" or "minilocus". Such "miniloci" are contained on plasmids or cosmids in the size range of 30 Kb and clearly have nothing like germline configuration. Krimpenfort, differs even more because it refers only to rearranged transgenes. Any teachings in Surani, Bruggemann or Krimpenfort, thus, must be confined to methods using miniloci or rearranged genes and cannot be extended to methods such as applicants' which utilize a substantially different transgenic mouse. None of the cited documents, thus, either alone or in any combination, can render obvious applicants' claims. Accordingly, the rejection over Surani, Bruggemann and Krimpenfort should be withdrawn.

Claim 1-3 stand rejected under § 103(a) also over Krimpenfort taken with United States patent 5,545,608 (Lonberg et al) ("Lonberg"). In the Examiner's view, Krimpenfort "discloses transgenic mice incapable of producing endogenous immunoglobulins" but fails to disclose mice with a transgene encoding human immunoglobulin genes. Further in the Examiner's view, Lonberg cures that deficiency by disclosing a method for producing human immunoglobulins in a transgenic mouse. In view of the claim amendments, applicants traverse.

Claims 2, 3, 46 and 47 are directed to methods utilizing a transgenic mouse characterized by endogenous immunoglobulin heavy chain loci in which all of the J segment genes are deleted to prevent rearrangement of the loci and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus. The transgenic mouse utilized in the claims also is characterized by inactivated endogenous immunoglobulin light chain loci in which one or more genes are deleted to prevent rearrangement of the loci and to prevent formation of a transcript of a rearranged immunoglobulin light chain locus. Krimpenfort neither teaches nor suggests such a mouse.

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Instead, Krimpenfort primarily relates to transgenic animals in which the expression of an endogenous "lymphatic polypeptide" is suppressed through dominant negative suppression, or allelic exclusion.

Krimpenfort also refers, however, somewhat cryptically to a method for preventing expression of an endogenous immunoglobulin locus by inserting a stop codon into the locus. It is common general knowledge that a stop codon operates during translation. Thus, Krimpenfort's system for preventing Ig expression aims at disrupting translation of a rearranged and transcribed immunoglobulin gene. That is not applicants' invention. In the methods of the invention, the endogenous Ig loci are modified so as to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged locus.

Krimpenfort, thus, does not disclose or even suggest the transgenic mice utilized in the methods of the invention. In the absence of any teaching in Krimpenfort or anywhere else in the art of the transgenic mice utilized in the methods of the invention, claim 2, 3, 46 and 47 are non-obvious regardless of any teaching that Lonberg may contain relating to the production of human immunoglobulins in mice. Accordingly, the rejection under § 103(a) should be withdrawn.

Rejection for Obviousness Type Double Patenting

Claims 1 and 2 stand rejected for obviousness type double patenting over claims 8-12 of United States patent 6,150,584 (Kucherlapati et al.) ("the '584 patent"). Applicants' cancellation of claim 1, without prejudice, obviates the rejection as the canceled claim. The Examiner asserts that claims 8-12 of the '584 patent represent species that fall within the broader claims in the instant application and that the species render obvious the genus. In view of the claim amendments, applicants traverse.

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Claims 2, 46 and 47 are directed to a method for producing an immunoglobulin comprising a fully human variable region utilizing a transgenic mouse that comprises a fragment of human chromosome 14 that does not include a gamma constant region. The claims, thus, explicitly exclude a method for producing a fully human IgG antibody. Claims 8-12 of the '584 patent, thus, no longer fall within the instant claims. Accordingly, the rejection for obviousness-type double patenting should be withdrawn.

In view of the above, applicants request withdrawal of the rejections and reconsideration and allowance of the amended claims.

Respectfully submitted,

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